

09-01-00

PATENT

JC853 U.S. PTO  
09/652376  
08/31/00

Attorney's Docket No.: U 012930-9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Patent Application  
Assistant Commissioner for Patents  
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of Inventor:

ARUN KUMAR SINHA

**WARNING:** The Declaration must name all of the actual inventor(s).

For (title):

AN IMPROVED PROCESS FOR THE PREPARATION OF 1-PROPYL-2,4,5-TRIMETHOXY-BENZENE FROM TOXIC  $\beta$ -ASARONE OF ACORUS CALAMUS OR FROM CRUDE CALAMUS OIL CONTAINING  $\beta$ -ASARONE

1. Type of Application

This new application is for a(n) (check one applicable item below):

- ☒ Original (nonprovisional)  
☐ Design  
☐ Plant

**WARNING:** Do not use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. 371(c)(4) unless the International Application is being filed as a divisional, continuation or continuation-in-part application.

**WARNING:** Do not use this transmittal for the filing of a provisional application.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date AUGUST 31, 2000 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL699731305US addressed to the: Assistant Commissioner of Patents, Washington, D.C. 20231

GERALDINE MARTI

(type or print name of person mailing paper)

*Geraldine Marti*  
(Signature of person mailing paper)

**NOTE:** Each paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 CFR 1.10(b).

**WARNING:** Certificate of mailing (first class) or facsimile transmission procedures of 37 CFR 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.

(Application Transmittal [4-1]—page 1 of 7)

EXPRESS MAIL LABEL  
NO.: EL699731305US

## 2. Benefit of Prior U.S. Application(s) (35 U.S.C. 119(e), 120, or 121)

**NOTE:** If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional application is claimed, then check the following item and complete and attach **ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED**.

**WARNING:** If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. 120, 121 or 365(c). (35 U.S.C. 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.

**WARNING:** When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional **must** be filed prior to the Saturday, Sunday or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).

- ☐ The new application being transmitted claims the benefit of prior U.S. application(s) and enclosed are **ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED**.

**NOTE:** If one of the following 3 items apply, then complete and attach **ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED** and a **NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION**.

- ☐ Divisional.  
☐ Continuation.  
☐ Continuation-in-Part (C-I-P).

## 3. Papers Enclosed That Are Required For Filing Date Under 37 CFR 1.53 (Regular) or 37 CFR 1.153 (Design) Application

20 Pages of specification

2 Pages of claims

1 Pages of Abstract

6 Sheets of drawing

- ☒ formal  
☐ informal

**WARNING:** **DO NOT** submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. Comments on proposed new 37 CFR 1.84. Notice of March 9, 1988 (1990 O.G. 57-62).

**NOTE:** "Identifying indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (5/8 inch) down from the top of the page." 37 C.F.R. 1.84(c).

(complete the following, if applicable)

- ☐ The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)". 37 C.F.R. 1.84(b).

4. **Additional papers enclosed**

- ☐ Preliminary Amendment
- ☐ Information Disclosure Statement (37 CFR 1.98)
- ☐ Form PTO-1449
- ☐ Citations
- ☐ Declaration of Biological Deposit
- ☐ Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
- ☐ Authorization of Attorney(s) to Accept and Follow Instructions from Representative
- ☐ Special Comments
- ☐ Other

5. **Declaration or oath**

- ☐ Enclosed  
executed by (*check all applicable boxes*)
  - ☐ inventor.
  - ☐ legal representative of inventor. 37 CFR 1.42 or 1.43
  - ☐ joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
    - ☐ This is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. *See item 13 below for fee.*
- ☒ Not Enclosed.

**WARNING:** *Where the filing is a completion in the U.S. of an International Application but where a declaration is not available or where the completion of the U.S. application contains subject matter in addition to the International Application the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.*

- ☒ Application is made by a person authorized under 37 CFR 1.41(c) on behalf of *all the above named inventor*. (The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently).

**NOTE:** *It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).*

- ☐ Showing that the filing is authorized. (*Not required unless called into question. 37 CFR 1.41(d).*)

6. **Inventorship Statement**

**WARNING:** *If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.*

The inventorship for all the claims in this application are:

- ☐ The same
- ☐ Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,

7. **Language**

**NOTE:** *An application including a signed oath or declaration may be filed in a language other than English. A verified English translation of the non-English language application and the processing fee of \$130.00 required by 37 CFR*

1.17(k) is required to be filed with the application or within such time as may be set by the Office. 37 CFR 1.52(d).

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).

- ☒ English  
☐ non-English  
☐ the attached translation is a verified translation. 37 CFR 1.52(d).

**8. Assignment**

- ☒ An assignment of the invention to COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH  
☐ is attached. A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.  
☒ will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters—one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

**WARNING:** A newly executed "CERTIFICATE UNDER 37 CFR 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993. 1150 O.G. 62-64.

**9. Certified Copy**

Certified copy of application

Country	Appln. No.	Filed
---------	------------	-------

from which priority is claimed

- ☐ is attached.  
☐ will follow.

NOTE: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 CFR 1.55(a) and 1.63.

NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. 120 is itself entitled to priority from a prior foreign application then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

**10. Fee Calculation (37 CFR 1.16)**

- A. ☒ Regular Application

---

Claims as Filed

---

Number Filed	Number Extra	Rate	Basic Fee 37 CFR 1.16(a) \$690.00
Total Claims (37 CFR 1.16(c))	12 - 20 = 0 x \$	18.00	
Independent Claims (37 CFR 1.16(b))	6 - 3 = 3 x \$	78.00	234.00
Multiple dependent claim(s), if any (37 CFR 1.16(d))	+ \$	260.00	

- ☐ Amendment cancelling extra claims enclosed.
- ☐ Amendment deleting multiple-dependencies enclosed.
- ☐ Fee for extra claims is not being paid at this time.

**NOTE:** *If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).*

Filing Fee Calculation \$

- B. ☐ Design application  
(\$310.00 — 37 CFR 1.16(f))

Filing Fee Calculation \$

- C. ☐ Plant application  
(\$480.00 — 37 CFR 1.16(g))

Filing Fee Calculation \$

**11. Small Entity Statement(s)**

- ☐ Verified Statement(s) that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is(are) attached or has been filed.

Filing Fee Calculation (50% of **A**, **B** or **C** above) \$

**NOTE:** *Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee. 37 CFR 1.28(a).*

**12. Request for International-Type Search (37 CFR 1.104(d)) (Complete, if applicable)**

- ☐ Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

**13. Fee Payment Being Made At This Time**

- ☒ Not Enclosed
- ☒ No filing fee is to be paid at this time. *(This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.)*

- ☐ Enclosed

☐ basic filing fee \$

- ☐ Recording assignment  
(\$40.00; 37 CFR 1.21(h)) (See attached "COVER SHEET FOR ASSIGNMENT ACCOMPANYING NEW APPLICATION.")
- ☐ Petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached.  
(\$130.00; 37 CFR 1.47 and 1.17(h)) \$
- ☐ For processing an application with a specification in a non-English language.  
(\$130.00; 37 CFR 1.52(d) and 1.17(k)) \$
- ☐ Processing and retention fee  
(\$130.00; 37 CFR 1.53(d) and 1.21(l))
- ☐ Fee for international-type search report  
(\$40.00; 37 CFR 1.21(e)). \$

**NOTE:** 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78, indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or the processing and retention fee of §1.21(l) must be paid within 1 year from notification under §53(d).

Total fees enclosed \$

#### 14. Method of Payment of Fees

- ☐ Check in the amount of \$
- ☐ Charge Account No. 12-0425 in the amount of \$

A duplicate of this transmittal is attached.

**NOTE:** Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b).

#### 15. Authorization to Charge Additional Fees

**WARNING:** If no fees are to be paid on filing, the following items should not be completed.

**WARNING:** Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.

- ☐ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. 12-0425.
  - ☐ 37 CFR 1.16(a), (f) or (g) (filing fees)
  - ☐ 37 CFR 1.16(b), (c) and (d) (presentation of extra claims)

**NOTE:** Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

- ☐ 37 CFR 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)
- ☐ 37 CFR 1.17 (application processing fees)

**WARNING:** While 37 CFR 1.17(a), (b), (c) and (d) deal with extensions of time under §1.136(a), this authorization should be made only with the knowledge that: "Submission of the appropriate extension fee under 37 C.F.R. 1.136(a) is to no avail unless a request or petition for extension is filed." (Emphasis added). Notice of November 5, 1985 (1060 O.G. 27)

- ☐ 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b))

*NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).*

*NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application ... prior to paying, or at the time of paying, ... issue fee". From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

**16. Instructions As To Overpayment**

- ☐ credit Account No. 12-0425  
☐ refund



*Signature of Attorney*

Reg. No.25,858

Tel. No.(212)708-1930

WILLIAM R. EVANS  
LADAS & PARRY  
26 WEST 61<sup>ST</sup> STREET  
NEW YORK, NEW YORK 10023

☐ **Incorporation by reference of added pages**

*(Check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED)*

- ☐ Plus Added Pages for New Application Transmittal Where Benefit of Prior U.S. Application(s) Claimed

Number of pages added \_\_\_\_

- ☐ Plus Added Pages for Papers Referred to in Item 4 Above

Number of pages added \_\_\_\_

- ☐ Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added \_\_\_\_

☒ **Statement Where No Further Pages Added**

*(If no further pages form a part of this Transmittal, then end this Transmittal with this page and check the following item:)*

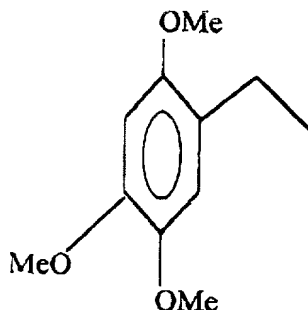
- ☒ This transmittal ends with this page.

U 012930-9

# AN IMPROVED PROCESS FOR THE PREPARATION OF 1-PROPYL-2, 4, 5-TRIMETHOXYBENZENE FROM TOXIC $\beta$ -ASARONE OF *ACORUS CALAMUS* OR FROM CRUDE CALAMUS OIL CONTAINING $\beta$ -ASARONE

## Field of the invention

The present invention relates to an improved process for the preparation of 1-Propyl-2,4,5-trimethoxybenzene of the formula I



I

from the toxic compound  $\beta$ -asarone of *Acorus calamus* or from crude calamus oil containing  $\beta$ -asarone. The present invention also relates to a process for the preparation of 1-Propyl-2,4,5-trimethoxybenzene from toxic compound  $\beta$ -asarone of *Acorus calamus* or from crude calamus oil containing  $\beta$ -asarone and useful as a new kind of aroma molecule. The present invention also relates to a process for the preparation of salicylamide based antipsychotic drug from 1-Propyl-2, 4, 5-trimethoxybenzene, and other uses thereof.

## Background of the invention

$\beta$ -asarone (cis-2,4,5-trimethoxy-1-propenylbenzene) is found in a number of plants such as *Orthodon calveriei* Level and *Acorus gramineus* (Nguyen, X. D.; Ladinh, M.; Vuviet, N.; Luudam, C. and Leclercq, P. A., J. of Essential Oil Research 7(1):111-112 (1995) and Perrett, S. and Whitfield, P. J., Phytotherapy Research 9(6):405-409 (1995)). Among all the plants, the highest percentage of  $\beta$ -asarone is present in tetraploid and hexaploid varieties of *Acorus calamus* (Rost, L. C. M., Planta Medica 36:350 (1979); Srivastava, M., Saxena, A. and Baby, P., Orient. J. Chem., 13(1): 97-98 (1997); Tang, W. and Eisenbrand, G., Chinese Drugs of Plant Origin, Springer-verlag, New York, 45-46 (1992) and Kaul, M. K., Medicinal Plants of Kashmir & Ladakh, Indus Publishing Company, 92-93 (1997)).

*Acorus calamus* Linn, a member of the family of Araceae, commonly known as "sweet flag", is a perennial plant (Grieve, M., A Modern Herbal, Tiger Books International, London, 726-729 (1998)) that grows in the wild along swamps, brooks, rivers and lakes worldwide. The plant is also cultivated widely in India, Pakistan, Bangladesh, China, Japan, Poland,

EXPRESS MAIL LABEL  
NO.: EL699731305US



Hungary, Yugoslavia, Bulgaria, USSR, Holland, USA and several other countries because of its varied medicinal activities and the great demand for its essential oil in the flavour and perfumery industries, in alcoholic beverages and for its antibacterial, antifungal and insecticidal properties (Treben, M., Health Through God's Pharmacy, Wilhelm Ennthal, Steyer, Austria, 12-14 (1986); Akhtar, H.; Virmani, O. P.; Popli, S. P.; Misra, L. N.; Gupta, M. M.; Srivastava, G. N., Abraham, Z. and Singh, A. K., Dictionary of Indian Medicinal Plants, CIMAP, RSM Nagar, Lucknow, 10-11 (1992); Motley, T.J., Economic Botany, 48:397-412 (1994) and Lawrence, B. M. and Reynolds, R. J., Perfumer & Flavorist 22(2):59-67 (1997)). However, photochemical reports on *Acorus calamus* reveals that the qualitative and quantitative composition of calamus oil and particularly the percentage of asarone is greatly affected by the location, growth stages and the species of *Acorus calamus*. A lot of discrepancy and variability has been noticed in asarone percentage of Asian and American calamus oil. It has been found that the oil of diploid plants (N. American) does not contain the carcinogenic compound  $\beta$ -asarone at all. The triploid race (E. European) contains limited amount of  $\beta$ -asarone varying from 3 to 8% and is therefore, usable in terms of both clinical effectiveness and safety (Stahl, E. and Keller, K., Planta Medica 43:128-140 (1981)). However, calamus oil originating from tetraploid or hexaploid varieties distributed extensively in Asian countries like India, Japan, Pakistan and China, contains a very high percentage of  $\beta$ -asarone varying from 70 to 90 % (Waltraud, G. and Schimmer, O., Mutation Research 121:191-194 (1983); Mazza, G., J. of Chromatography 328:179-206 (1985); Nigam, M. C.; Ateeque, A.; Misra, L. N. and Ahmad, A., Indian Perfumer 34: 282-285 (1990) and Bonaccorsi, I.; Cortroneo, A.; Chowdhury, J. U. and Yusuf, M., Essenze Derv. Agrum, 67(4): 392-402 (1997)). The higher percentage of  $\beta$ -asarone is experimentally proved to be carcinogenic in animals and was found to induce tumours in the duodenal region after oral administration (Taylor, J. M.; Jones, W. I.; Hogan, E. C.; Gross, M. A.; David, D. A. and Cook, E. L., Toxicol. Appl. Pharmacol. 10:405 (1967); Keller, K.; Odenthal, K. P. and Leng, P. E., Planta Medica 1:6-9 (1985) and Riaz, M.; Shadab, Q.; Chaudhary, F. M., Hamdard Medicus 38(2): 50-62 (1995)). In addition,  $\beta$ -asarone has also shown chromosome damaging effect on human lymphocytes *in-vitro* after metabolic activation (Abel, G., Planta Medica 53(3): 251-253 (1987)). As a result, the use of this well known medicinal plant which had been in use for many years, is now prohibited in flavour, perfumery and human food (Harborne, J. B. and Baxter, H., Phytochemical Dictionary: A Handbook of Bioactive Compounds from Plants, Taylor & Francis Ltd., Washington DC, 474 (1993) and McGuffin,

M., American Herbal Products Association's Botanical Safety Handbook, CRC Press, Inc., Boca Raton Florida, USA, 231 (1997)).

The oil and extracts of *Acorus calamus* have been reported to have numerous pharmacological activities. Some of the active ingredients found therein are glucosides, sitosterol (Patra, A. and Mitra, A. K., Indian J. Chem., Sec B, 17B:412 (1979), amino acids, acoramone (Patra, A. and Mitra, A. K., J. of Natural Products 44(6):668-669 (1981), flavones, fatty acid, sesquiterpene named calamonone (Wu, Li.; Xiang, T.; Liu, T.; Li, M.; Gao, Z. and Meng, X., Bopuxue Zazhi 15 (3):249-251 (1998) and triterpenoid saponins (Rai, R.; Siddiqui, I. R. and Singh, J., Indian J. Chem., Sec B, 37 B(5). 473-476 (1998)) Modern applications of the *Acorus calamus* plant include its use in cleansing of facial skin (Horste, B.; Sarma, I.; Gercikovs, I. and Gordejeva, V., L. V. Patent No. 92-920022, issued May 28, (1992); germination inhibitors (Nawamaki, K. and Kuroyanagi, M., Phytochemistry 43 (6):1175-1182, (1996); in formulation for alcoholic bitters (Sargunas, G.; Daniuniene, G.; Talacka, C., and Aleksionas S., L. T. Patent No. 36793, issued Jan 25, (1996) and for the prevention and improvement of vision disorders (Mihara, T., JP Patent No. 10324636 A2, issued Dec 8, (1998)).

*Acorus calamus*, known as "vaich" in Hindi, has also been credited with many medicinal properties from ancient times in Ayurvedic system of India (Vohora, S. B.; Shah, S. A. and Dandiya, P. C., J. of Ethnopharmacology 28(1): 53-62 (1990); Rastogi, R. P. and Mehrotra, B. N., Compendium of Indian Medicinal Plants, 1:1, (1990), C. S. I. R., New Delhi and Asolkar, L. V.; Kakkar, K. K. and Chakre, O. J., Glossary of Indian Medicinal Plants with Active Principles, Publications & Information Directorate (C. S. I. R.), New Delhi, Part-I, 18-20 (1992)). It is known for more than 2000 years in China for treating a number of disorders (Albert, Y. L., Encyclopædia of Common Natural Ingredient Used in Food, Drugs and Cosmetics, ed. John Wiley & Sons Inc. New York, 111-112 (1996)). However, all the above uses and medicinal potential of *Acorus calamus* have been hampered because of carcinogenic effect of  $\beta$ -asarone (Opdyke, D. L. J., Food Cosmet. Toxicol., 15: 623, (1997)).  $\alpha$ -Asarone is also reported to be fatal in rats (Lopez, M. L.; Hernandez, A.; Chamorro, G. and Mendoza, F. T., Planta Medica 59(20):115-120 (1993) and Chamorro, G.; Salazar, M.; Salazar, S. and Mendoza, T., Revista-de-Investigacion-Clinica 45(6):597-604 (1993)). As a result, countries such as India, Pakistan, Bangladesh, Japan and China where plants of tetraploid and hexaploid origin contain 70 to 90%  $\beta$ -asarone are most affected by the prohibition on the use of calamus oil.

The levels of  $\beta$ -asarone can be easily detected by IR-spectroscopy (Stahl, E. and Keller, K., *Pharmazie* 36(1):53-57 (1981); HPTLC (Narayana, D. B. A.; Raghuvanshi, P.; Agarwal, S. and Srinivas, K. S., *Indian Drugs* 32(6):254-257 (1995); densitometry (Tamas, M.; Oprean, R. and Roman, L., *Farmacia (Bucharest)* 44 (5-6): 13-21 (1996)); gas chromatography (Baxter, R. M.; Dandiya, P. C.; Kandel, S. I.; Okanya, A. and Walker, G. C., *Nature* 185:466-467 (1960) and Spilkova, J. T.; Tomasch, J.; Vavra R. and Dusek, J., *Ceska Slov. Farm.*, 45 (3): 146-148 (1996)) and GC-MS (Oprean, R.; Tamas, M. and Roman, L., *J. Pharm. Biomed. Anal.*, 18 (1,2): 227-234 (1998)).

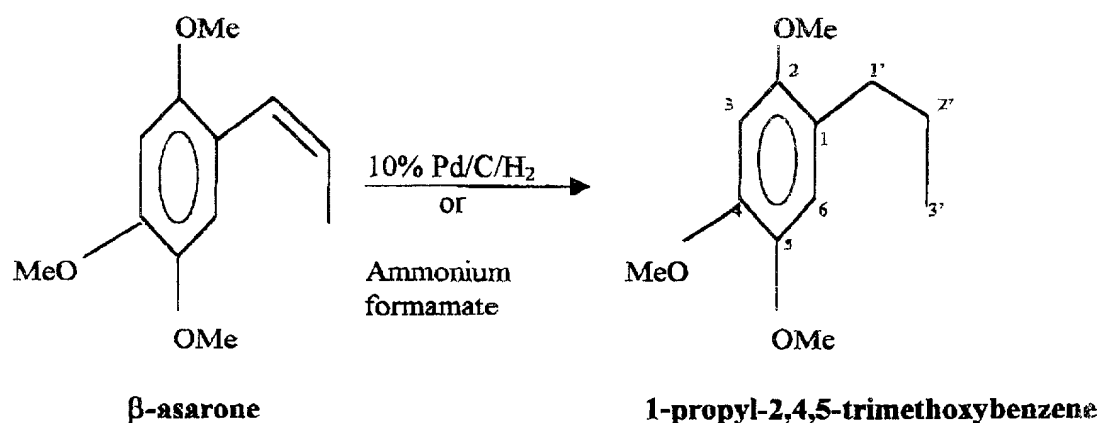
Separation of  $\beta$ -asarone from calamus rhizomes (*americanus* var.) by supercritical extraction (Stahl, E. and Keller, K., *Planta Medica* 47 (2): 75-78 (1983)) or by raising plants on alkaline soil (Chowdhary, A. R.; Gupta, R. C. and Sharma, M. C., *Indian Perfumer* 41 (4): 154-156 (1997)) have been developed. However, these methods do not effectively lower the high percentage (70 to 90 %) of asarone content of tetraploid or hexaploid varieties. It is therefore imperative to provide a simple chemical process by which  $\beta$ -asarone or crude calamus oil can be easily modified to reduce its carcinogenic effect rather than by reduction in the percentage of asarones by any other means. While supercritical gas extraction of calamus oil (*americanus* variety) with fractionated separation has been reported (Keller, K. and Stahl, E., *Planta Medica* 47(2): 71-74 (1983)) to make  $\beta$ -asarone free calamus oil, fractionation will not be cost effective with tetraploid or hexaploid varieties having very high percentage of  $\beta$ -asarone (70 to 90 %).

Interest in development of a simple and economical chemical process to reduce the toxicity of carcinogenic compound  $\beta$ -asarone by elimination of side double bond continues to be strong as evidenced by numerous literature reports that show that the double bond of asarone is responsible for bioactivity and photooxidation. A detailed literature survey reveals that calamus oil has been found active as antigonadal, antifeedant and growth inhibitory in insects. The activities of calamus oil are found due to the presence of double bond in the alkyl side chain and cis configuration of  $\beta$ -asarone (Saxena, B. P.; Koul, O.; Tikku, K.; Atal, C. K. and Opendar, K., *Nature, London*, 270(5637): 512-513 (1977); Koul, O., *Sci. Acad. Medal Lectures*, Ed. INSA, New Delhi, India, 62 (1979) and Koul, O.; Smirle, M. J. and Isman, M. B., *J. Chem. Ecol.* 16:1911-1920 (1990)). The side double bond forms asarone epoxide and asarone diol which is identified in the insect excreta of *Peridroma saucia* larvae (Noctuidae: Lepidoptera) (Koul, O.; Smirle, M. J.; Isman, M. B. and Szeto, Y. S., *Experientia* 46:1082-1084 (1990)). The double bond of  $\beta$ -asarone is also found to be photosensitive and while

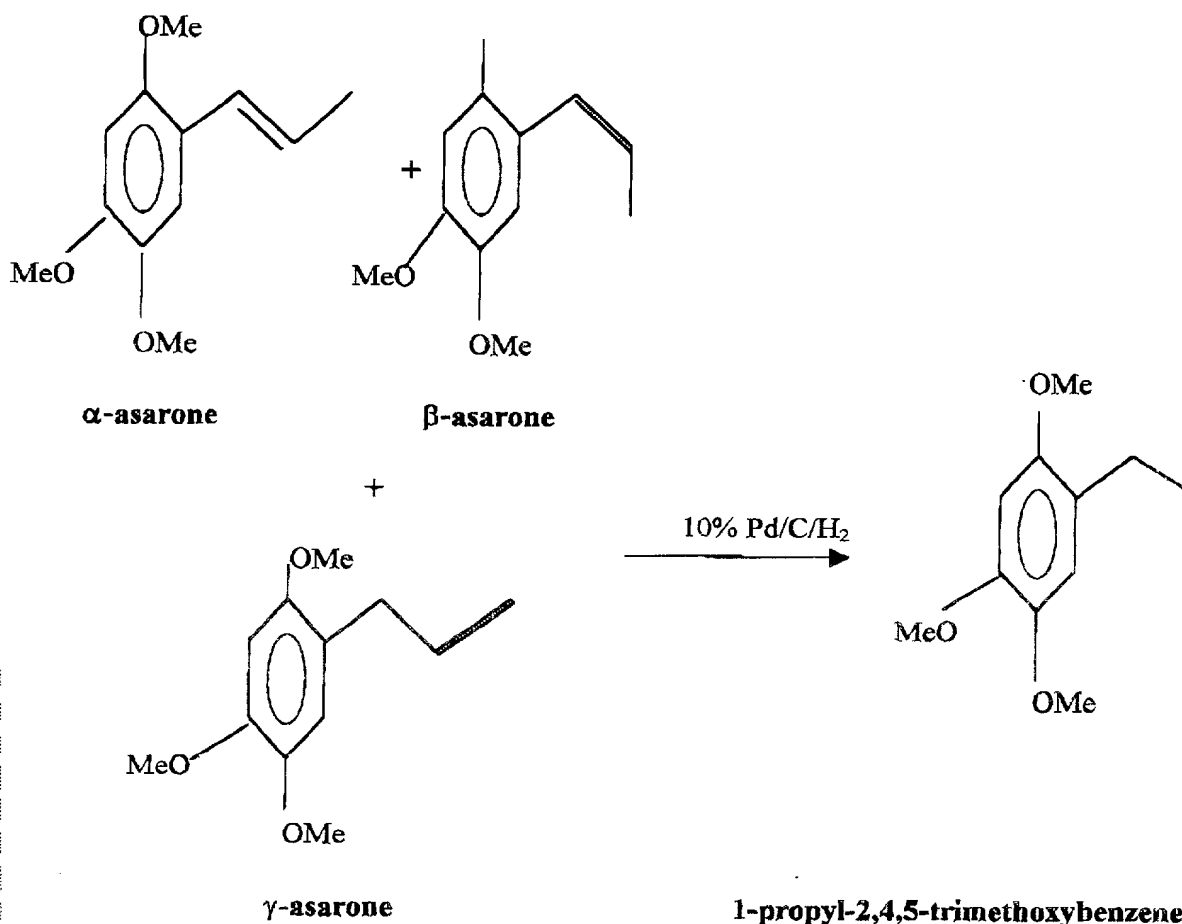
standing the calamus oil on long storage without exclusion of air and light, the oil got contaminated with photo-oxidised products such as asaraldehyde and dimer (Saxena, D. B. and Mukerjee, S. K., Indian J. Chemistry, Sec B, 24 B: 683-684 (1985)). Recently, a number of photoxidised product formations were also studied by light induced transformation of  $\beta$ -asarone in ethanolic solutions (Lander, V. and Schreier, P., Flavour Fragrance J. 6(1).21-28 (1991)). Based on the above survey, it appears logical to develop a convenient chemical process for utilising the side double bond of  $\beta$ -asarone to reduce its toxicity.

It is reported that the side double bond of isolated  $\beta$ -asarone of *Acorus calamus* or crude calamus oil is reduced either over Pd, Pt, Pd(OH)<sub>2</sub>, PtO<sub>2</sub>, BaSO<sub>4</sub>/Pd, Raney nickel and ammonium formate to obtain 1-Propyl-2,4,5-trimethoxybenzene with improved properties such as an aroma that is better than the pungent smell of  $\beta$ -asarone (Joseph G. C.; Claire, D T.; John, P. L., Ranbir, K. B.; Paul, L. and Jan, R. F., J. Med. Chem. 32:2210:2214 (1989); Christopher, I.; Fincham, M. H.; David, R. H.; David, C. H., John, C. O.; Giles, S. R.; David, C. R. and Edward, R., J. Med. Chem. 35:1472-1484 (1992) and Tomoyuki, Y.; Ryo, N.; Toru, K.; Shinichi, T.; Tamako, N., Tokio, Y. and Toshiyasu, M., J. Med. Chem. 40:1252-1257 (1997)).

The reaction schemes of the processes are given below:



**SCHEME I**

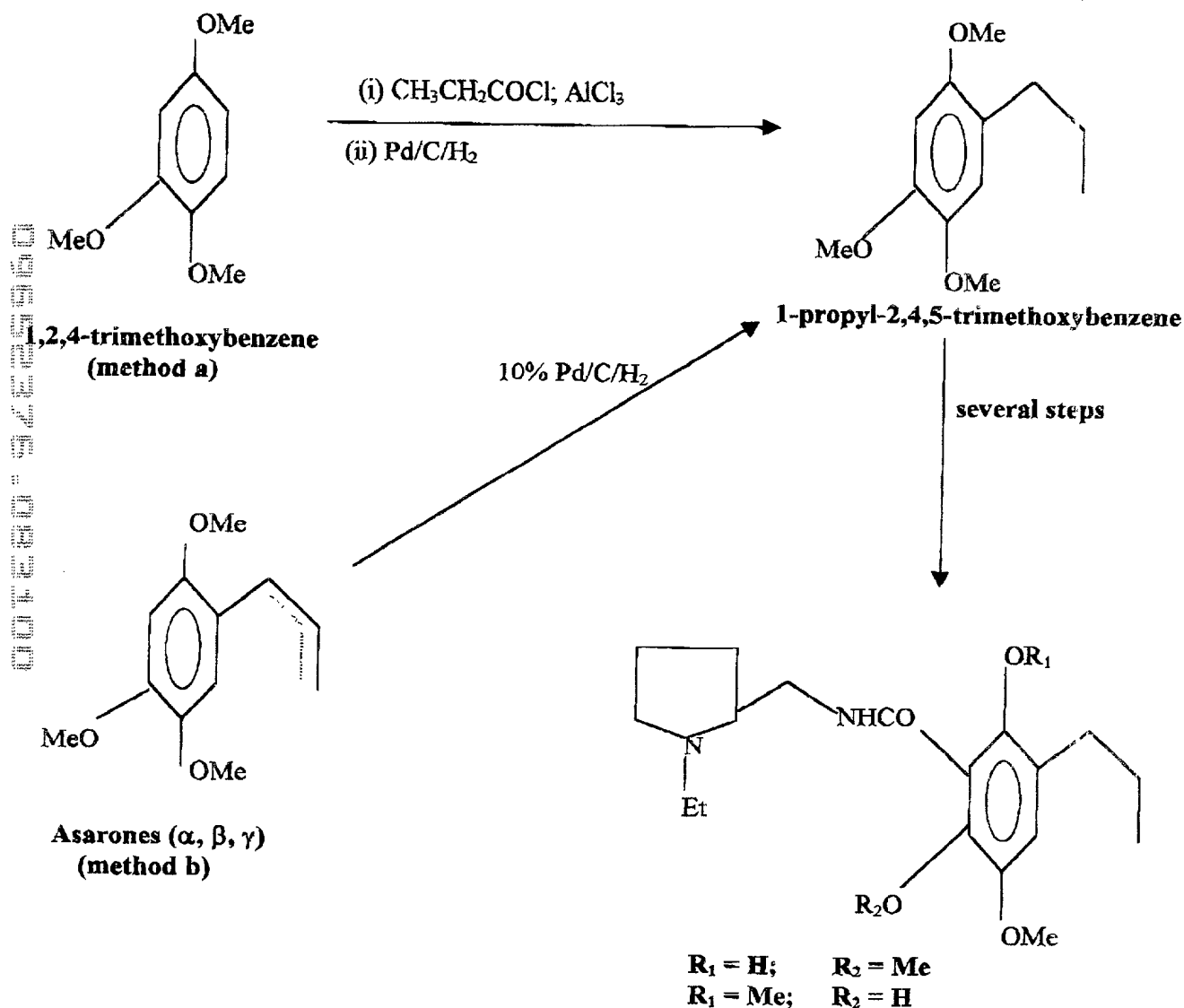


### SCHEME II

The olfactory assessment of 1-Propyl-2,4,5-trimethoxybenzene is performed as per Indian standard of 2284, 1997 (Bureau of Indian Standard, Manak Bhavan, 9 Bahadur Shah Zafar Marg, New Delhi). The odour effect perceived by the olfactory nerves on smelling a strip impregnated with an oil is revealed as sweet, ylang, slightly spicy and fruity thereby enabling use as multipurpose additives in the areas of mouthwash, tooth paste, antiseptic soap products, chewing gum flavour and little in spicy products. In addition, it was observed that the product 1-Propyl-2,4,5-trimethoxybenzene is a simple and an economical starting material for synthesis of salicylamide based antipsychotic drugs (5,6-dimethoxy-N[(1-ethyl-2-pyrrolidinyl)methyl]-3-propylsalicylamide).

The salicylamide derivative displays high and stereoselective affinity for the [3H] spiperone and [3H] raclopride binding sites *in vitro* (dePaulis, T.; Kumar, Y.; Johansson, L.; Ramsby, S.; Florvall, L.; Hall, H.; Angeby, M. K. and Ogren, S. O., J. Med. Chem. 28:1263-1269 (1985) and dePaulis, T.; Kumar, Y.; Johansson, L.; Ramsby, S.; Hall, H.; Sallemark, M.; Angeby, M. K. and Ogren, S. O., J. Med. Chem. 29:61-69 (1986)). Recently, Hogberg T.,

Stefan, B.; Tomas, D. P.; Lars, J.; Peter, S.; Hakan, H. and Ogren, S. O., J. Med. Chem. 33: 1155-1163 (1990) have synthesized a series of 3-substituted salicylamide derivatives in which the presence of 3-propyl group and 5,6-dimethoxy group at salicylamide ring shows a very high and stereoselective affinity for the dopamine-D<sub>2</sub> receptor. However, the reported synthesis for salicylamide derivative involved several steps in which intermediate 1-Propyl-2,4,5-trimethoxybenzene is itself synthesized in two steps by Friedel-Craft acylation of an expensive material 1,2,4-trimethoxybenzene with propylchloride followed by catalytic hydrogenation with an overall in lower yield (reaction scheme given below as Scheme III).



**SCHEME III**

### Objects of the invention

The main object of the present invention is to develop a process for the preparation of 1-propyl-2,4,5-trimethoxybenzene from high toxic compound  $\beta$ -asarone present in the  $\beta$ -asarone bearing varieties of *Acorus calamus* or from crude calamus oil containing  $\beta$ -asarone obtained therein.

It is another object of the invention to develop a process for the preparation of 1-propyl-2,4,5-trimethoxybenzene which is useful as a new kind of aroma molecule with multifarious applications.

It is another object of the invention to develop a process for the preparation of 1-propyl-2,4,5-trimethoxybenzene which is useful as a starting material for salicylamide based antipsychotic drugs.

Another object of the present invention is to provide a simple process for isolation of  $\beta$ -asarone in high purity from *Acorus calamus* oil.

Still another object of the present invention is to provide a simple process for the preparation of 1-Propyl-2,4,5-trimethoxybenzene by catalytic reduction of above isolated  $\beta$ -asarone.

Yet another object of the present invention is to provide a simple and an inexpensive process for the preparation of 1-Propyl-2,4,5-trimethoxybenzene by direct reduction of calamus oil in which the percentage of asarones (including  $\alpha$ ,  $\beta$  and  $\gamma$ -asarone) go upto 90 % in tetraploid or hexaploid varieties of *Acorus calamus* oil.

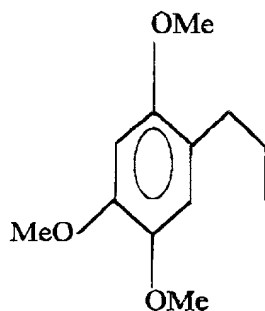
Yet another object of the present invention is to provide 1-Propyl-2,4,5-trimethoxybenzene as an inexpensive and simple starting material for synthesis of several drugs, for example salicylamide based antipsychotic drugs.

Yet another object of the present invention is to eliminate or minimize the toxicity of calamus oil of tetraploid or hexaploid varieties of Asian countries, thereby enhancing the profitable use thereof.

Yet another object of the present invention is to provide a simple reduction process in converting essential oils of other asarones rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis* into useful products such as 1-Propyl-2,4,5-trimethoxybenzene for use in the flavour, perfumery and pharmaceutical industries.

### Summary of the invention

Accordingly, the present invention relates to a process for the preparation of 1-Propyl-2, 4, 5-trimethoxybenzene of the formula I useful as a aroma molecule and as a starting material and intermediate for preparation of various drugs,



I

the said process comprising the steps of

- (a) providing crude calamus oil or  $\beta$ -asarone in a solvent selected from the group consisting of ethanol, methanol, THF, DCM, Toluene and chloroform
- (b) hydrogenation of the solution in the presence of a catalyst selected from the group comprising of Pd/C, Pt, Pd(OH)<sub>2</sub>, Raney nickel and ammonium formate at a pressure in the range of 10 – 40 psi hydrogen gas and at a temperature in the range of 15 - 40°C;
- (c) filtering the catalyst and removing the solvent under reduced pressure in the range of 10 – 100 mm Hg;
- (d) subjecting the reduced calamus oil to column or silica gel chromatography using an eluent to obtain the desired product in liquid form with 85 – 97 % purity.

In one embodiment of the invention the catalyst comprises 5 – 10 % Pd/C.

In another embodiment of the invention, the calamus oil used is of tetraploid or hexaploid origin.

In yet another embodiment of the invention, a new kind of honey and rose aroma is detected in the case of reduced calamus oil.

In yet another embodiment of the invention, a new kind of sweet, ylang, slightly spicy and fruity aroma is detected in case of 1-Propyl-2,4,5-trimethoxybenzene.

In another embodiment of the invention, the reduced calamus oil is useful in the toiletry soap, shaving cream and tobacco products.

In another embodiment, the invention relates to the use of 1-Propyl-2,4,5-trimethoxybenzene as a multipurpose additive in mouthwash, tooth paste, antiseptic soap products, chewing gum flavour and in spicy products.



In a further embodiment, the invention relates to the use of 1-Propyl-2,4,5-trimethoxybenzene as an inexpensive and simple starting material for the preparation of the 3-propyl -5,6-dimethoxysalicylamide based antipsychotic drug 5, 6 - dimethoxy - N [(1 - ethyl - 2 - pyrrolidinyl) methyl] - 3 - propylsalicylamide.

In another embodiment, the invention relates to the conversion of 1-Propyl-2,4,5-trimethoxybenzene to products which can be used for flavour, perfumery industries and as starting material for various important drugs and for new organic compounds by bromination, oxidation, reduction, coupling reaction, allylic hydroxylation, dimerisation, formylation, Grignard reaction, oxymercuration- demercuration, demethylation, alkylation and epoxidation.

In a further embodiment of the invention, the crude calamus oil is extracted from asarone rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis*.

In another embodiment of the invention, the toxicity of the reduced calamus oil is two times less than that of the starting crude calamus oil.

In another embodiment of the present invention a simple catalytic hydrogenation of either  $\beta$ -asarone of *Acorus calamus* or calamus oil is described to obtain 1-Propyl-2,4,5-trimethoxybenzene or reduced calamus oil with a new kind of sweet, fruity, spicy and honey and rosy aroma for use flavour, perfumery and pharmaceutical industries.

In yet another embodiment of the present invention a simple catalytic process is described to convert other asarones rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis* into useful products such as 1-Propyl-2,4,5-trimethoxybenzene for various applications.

#### **Brief description of the accompanying drawings.**

Figure 1 is the UV spectra of 1-Propyl-2,4,5-trimethoxybenzene and its comparison with  $\beta$ -asarone (2,4,5-trimethoxy-1-propenylbenzene).

Figure 2 is a gas chromatogram of  $\beta$ -asarone with minor presence of  $\alpha$ -asarone.

Figure 3 is a gas chromatogram of 1-Propyl-2,4,5-trimethoxybenzene.

Figure 4 is  $^1\text{H}$  NMR (300 MHz) of 1-Propyl-2,4,5-trimethoxybenzene in  $\text{CdCl}_3$ .

Figure 5 is  $^{13}\text{C}$ -NMR (75.4 MHz) of 1-Propyl-2,4,5-trimethoxybenzene in  $\text{CdCl}_3$ .

Figure 6 is the electro spray (ES) mass spectrum of 1-Propyl-2,4,5-trimethoxybenzene (MW 210).

#### **Detailed description of the invention**

The present invention affords a single step synthesis of 1-Propyl-2,4,5-trimethoxybenzene by catalytic hydrogenation of calamus oil or  $\beta$ -asarone (cis-2,4,5-trimethoxy-1-propenylbenzene). The UV-vis spectra of 1-Propyl-2,4,5-trimethoxybenzene clearly show the loss of side double bond, as there was shift in absorbance by 13 nm (Fig. 1). In the first approach,  $\beta$ -asarone is isolated by column chromatography of calamus oil which gave a single spot of  $\beta$ -asarone with  $R_f$  0.63 (hexane: benzene/toluene: ethylacetate:: 1:1:0.1) on silica gel TLC plate but its gas chromatography ( $t_r$  = 20.16 min) (performed on a Shimadzu-GC-14B gas chromatograph with the following conditions: SE-30 column, 30 m x 0.25 mm; injector 250°C; FID detector 230 °C; temp. programme 40 (hold for 2 min.) to 220°C (hold for 10 min.), 10°C min<sup>-1</sup>; vol. 1  $\mu$ l; N<sub>2</sub> flow 30ml/min; H<sub>2</sub> flow 40ml/min, air flow 300ml/min.; split injection ratio 1:30) has shown the purity in 94% (Fig. 2) with minor presence of other isomers  $\alpha$ -asarone ( $t_r$  = 20.87 min) and/or  $\gamma$ -asarone. Since it was not very easy to separate  $\beta$ -asarone completely from  $\alpha$  and  $\gamma$ -asarone on column chromatography due to the close resemblance in their structure, no efforts were made for further purification.  $\beta$ -asarone of 94 % was used as such for catalytic reduction which gave a single spot of 1-Propyl-2,4,5-trimethoxybenzene with  $R_f$  0.69 (hexane: benzene/toluene: ethylacetate::1:1:0.1) on silica gel TLC plate and its purity was found 99% (Fig. 3) on gas chromatography ( $t_r$  = 19.78 min) indicating the reduction of  $\beta$ -asarone along with  $\gamma$  and  $\alpha$ -asarone.

**Isolation of  $\beta$ -asarone from *Acorus calamus*:** The pale yellow calamus oil (17.00 g) was chromatographed over silica gel using hexane as eluent to remove unwanted non-polar compounds. Subsequent elution with hexane-benzene mixture with increasing proportion of benzene gave 13.94 g of a pure liquid with 82 % yield (w/w) with  $R_f$  0.63 on silica gel TLC plate (hexane: benzene/toluene: ethylacetate = 1:1:0.1) whose electrospray (ES)-mass spectrum gave a molecular ion at  $m/e$  208 ( $M^+$ , 100), 193 ( $M^+$ - Me, 46), 165 ( $M^+$ - C<sub>3</sub>H<sub>7</sub>, 24), suggesting the molecular formula C<sub>12</sub>H<sub>16</sub>O<sub>3</sub> in good agreement with the observation of 12 signals with peak at  $\delta$  125.5 (C-1'), 124.7 (C-2') and 14.5 (C-3') for side propenyl group and rest carbons at 151.4 (C-2), 148.5 (C-4), 142.3 (C-5), 118.0 (C-1), 114.1 (C-6), 97.6 (C-3) and 56.5, 56.2 & 55.9 (3-OCH<sub>3</sub>) on the <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.4 MHz). The IR spectrum showed strong absorption at 1608 cm<sup>-1</sup>, indicating the presence of an olefinic group and rest are at 2937, 2835, 1583, 1512, 1465, 1321, 1213, 1119, 1037, 965 and 859 cm<sup>-1</sup>. The <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) signals showed a dd at  $\delta$  6.50 (1H, J=15.8 Hz and 1.5 Hz, H-1'), dq at 5.78 (1H, J=6.5 Hz and 15.8 Hz, H-2') and 1.85 (3H, dd, J=6.5 Hz and 1.5 Hz, H-3') due to proton of propenyl side chain and rest protons at 6.84 (1H, s, H-6), 6.53 (1H, s, H-3), and

3.88, 3.83 and 3.79 (s, 3H, each, 3-OCH<sub>3</sub>). UV  $\lambda_{\text{max}}$  MeOH nm (log  $\epsilon$ ): 269 (2.36), 301 (4.01). On the basis of above spectral data and comparing with reported literature (Gonzalez, M. C.; Sentandreu, M. A.; Rao, K. S.; Zafra, M. C. and Cortes, D., *Phytochemistry* 43:1361-1364 (1996)), the liquid was identified as  $\beta$ -asarone in 94% purity (by GC) (Fig. 2)

**Synthesis of 1-Propyl-2,4,5-trimethoxybenzene from  $\beta$ -asarone:** The  $\beta$ -asarone (6.00 g, 0.029 mol) in 160 ml of ethanol is stirred with 10% palladium on activated charcoal (0.80 g) and ammonium formate (17.00 g, 0.27 mol) at room temperature under nitrogen atmosphere till the disappearance of starting material. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water and the ethyl acetate layer washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. Evaporation of filtrate left a liquid, which was chromatographed, on silica gel using hexane-benzene mixture with increasing proportion of benzene as the eluent. The eluate was evaporated to give 5.87 g (97%) of a clear sweet and pleasant liquid with  $R_f$  0.69 (hexane: benzene/toluene: ethylacetate = 1:1:0.1) which solidified below 0° C. The <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of liquid showed an expected shift of proton of propyl side chain which appeared at  $\delta$  2.5 (2H, t, C-1'), 1.6 (2H, m, C-2') and 0.9 (3H, t, C-3') and rest protons at 6.72 (1H, s, H-6), 6.62 (1H, s, H-3) and 3.76 to 3.68 (9H, s, 3-OCH<sub>3</sub>). The mass spectrum of liquid showed a molecular ion at  $m/e$  210 ( $M^+$ , 39), 181 ( $M^+$ -C<sub>2</sub>H<sub>5</sub>, 100), 167 ( $M^+$ -C<sub>3</sub>H<sub>7</sub>, 5), 151 ( $M^+$ -OCH<sub>3</sub>+CO, 29), 136 ( $M^+$ -C<sub>3</sub>H<sub>7</sub>+OCH<sub>3</sub>, 10) which IR spectrum showed strong absorption at 2958, 2870, 1512, 1464, 1398, 1205, 1124, 1040, 978 and 843 cm<sup>-1</sup> with disappearance of olefinic absorption (1608 cm<sup>-1</sup>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) of liquid also showed expected shift of propyl side signals of C-1', C-2' and C-3' which appeared at  $\delta$  31.6 (C-1'), 23.3 (C-2') and 13.79 (C-3') and rest at  $\delta$  151.4 (C-2), 147.4 (C-4), 142.7 (C-5), 122.7 (C-1), 114.3 (C-6), 98.0 (C-3) and 56.5, 56.2 & 56.0 (3-OCH<sub>3</sub>). UV  $\lambda_{\text{max}}$  MeOH nm (log  $\epsilon$ ): 288 (4.28). A shift by 13 nm in UV-vis spectra of product was observed from 301 nm to 288 nm (as conjugation of double bond of starting material asarone was reduced to single bond) with complete disappearance of peak 269 nm (Fig 1). On the basis of <sup>1</sup>H NMR (Fig. 4), <sup>13</sup>C NMR (Fig. 5) and Mass (Fig. 6) spectral data, the above liquid was identified as 1-Propyl-2,4,5-trimethoxybenzene of Formula I in 99 % purity (by GC) (Fig. 3).

**Synthesis of 1-Propyl-2,4,5-trimethoxybenzene from crude oil of *Acorus calamus*:** In this method 42.00 g of crude calamus oil in 300 ml methanol was hydrogenated with 10 % Pd/C (4.80 g) at 10-40 psi at room temperature till the disappearance of starting material. The catalyst was filtered and the solvent was removed under reduced pressure, which afforded

39.9 g (95 w/v) of reduced oil. Column purification of reduced oil on silica gel column using above eluent system (hexane-benzene mixture) gave a liquid 35.76 g in 85 % yield (w/w). The  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of liquid appeared at  $\delta$  d 2.4 (2H, t, C-1'), 1.6 (2H, m, C-2'), 0.9 (3H, t, C-3'), 6.81 (1H, s, H-6), 6.32 (1H, s, H-3) and 3.84 to 3.78 (9H, s, 3-OCH<sub>3</sub>). The GC, Mass spectra and UV-vis spectra of liquid confirmed the formation of 1-Propyl-2,4,5-trimethoxybenzene.

**Synthesis of salicylamide based antipsychotic drug (5,6-dimethoxy-N[(1-ethyl-2-pyrrolidinyl)methyl]-3-propylsalicylamide:** Synthesis of this drug is reported by Thomas, H.; Stefan, B.; Tomas, D. P.; Lars, J.; Peter, S.; Hakan, H., and Orgen S. O., *J. Med. Chem.* 33: 1155-1163 (1990) and involved several steps, the details of which are given below:

- i. **2,4,5-trimethoxypropiophenone:** Aluminium chloride (18.6 g, 0.14 mol) was added to a solution of 1,2,4-trimethoxybenzene (23.4 g, 0.14 mol) and propionyl chloride (11.4 g, 0.14 mol) in 250 ml of  $\text{CH}_2\text{Cl}_2$  at  $10^\circ\text{C}$ . After stirring for 1 hour, standard work up and recrystallisation from MeOH gave 25.0 g (80%) of pure product (i), mp  $108 - 110^\circ\text{C}$ . Anal ( $\text{C}_{12}\text{H}_{16}\text{O}_4$ )  $\text{C}_{12}\text{H}_{16}\text{O}_4$ . (Other spectral data such as NMR, Mass is not mentioned).
- ii. **1-propyl-2,4,5-trimethoxybenzene:** It was prepared by hydrogenation (4.5 l  $\text{H}_2$ , 0.2 mol) of the corresponding propiophenone (i) (22.4 g, 0.1 mol) in 350 ml of MeOH at normal pressure with palladium on charcoal (5%, 2.3 g) as catalyst. Filtration and evaporation gave 20 g (0.1 mol) of an oil (ii) which lithiated directly. (Spectral data such as NMR, Mass is not given).
- iii. **3-propyl-2,5,6-trimethoxybenzoic acid:** It was prepared by addition of butyllithium to a solution of 1-propyl-2,4,5-trimethoxybenzene (ii) in anhydrous THF under  $\text{N}_2$  at  $20 - 30^\circ\text{C}$ . After stirring for 1.5 hours the reaction mixture was poured into solid carbon dioxide in  $\text{Et}_2\text{O}$ . Water was added and the phases were acidified with concentrated HCl and extracted with  $\text{CH}_2\text{Cl}_2$ . Evaporation of the solvent provided a crude acid (iii) contaminated with some pentanoic acid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.8 (s, 1), 3.8 – 3.9 (3s, 9), 2.4 (t, 2), 1.6 (m, 2), 0.9 (t, 3). Characterised as primary amide (iii), mp  $130 - 131^\circ\text{C}$  (i-Pr<sub>2</sub>O).
- iv. **(S)-3-propyl-N-[(1-ethyl-2-pyrrolidinylmethyl)-2,5,6-trimethoxybenzamide]:** A solution of 3-propyl-2,5,6-trimethoxybenzoic (iii), thionyl chloride and a few drops of dimethylformamide in toluene was stirred at  $60^\circ\text{C}$  for 1 hour. The solvent was evaporated and the residue was dissolved in  $\text{CHCl}_3$  and evaporated again. The residual

acid chloride was dissolved in  $\text{CHCl}_3$  and a solution of (S)-2-(aminomethyl)-1-ethylpyrrolidone in 40 ml of  $\text{CHCl}_3$  was added. The temperature rose to  $50^\circ\text{C}$  during addition. After stirring for 30 minutes, the solvent was evaporated and the residue was partitioned between 1M NaOH and  $\text{Et}_2\text{O}$ . After additional extraction of the aqueous phase with  $\text{Et}_2\text{O}$ , the combined ethereal extract were dried and evaporated to give (S)-3-propyl-N-[(1-ethyl-2-pyrrolidinylmethyl)]-2,5,6-trimethoxybenzamide (iv) in 32 % yield, mp  $68-70^\circ\text{C}$ .

- v. **(S)-5,6-dimethoxy-N-[(1-ethyl-2-pyrrolidinylmethyl)]-3-propylsalicylamide and isomer (S) - 2, 5 - dimethoxy - N - [(1 - ethyl - 2 - pyrrolidinylmethyl) - 3 - propylsalicylamide]:** A solution of (iv) (10.0 g, 0.027 mol) and HCl (0.027 mol in  $\text{Et}_2\text{O}$ ) in 250 ml of  $\text{CH}_2\text{Cl}_2$  was treated with  $\text{BBr}_3$  (6.8 g, 0.027 mol) in 50 ml of  $\text{CH}_2\text{Cl}_2$  at  $10^\circ\text{C}$ . The reaction mixture was stirred for 2 hours at  $20^\circ\text{C}$  and quenched with 100 ml of 2M  $\text{NH}_3$ . Extraction with  $\text{CH}_2\text{Cl}_2$ , drying ( $\text{Na}_2\text{SO}_4$ ), and evaporation of the solvent gave 9.2 g of (S)-5,6-dimethoxy-N-[(1-ethyl-2-pyrrolidinylmethyl)]-3-propylsalicylamide and isomer (S) - 2, 5 - dimethoxy - N - [(1 - ethyl - 2 - pyrrolidinylmethyl) - 3 - propylsalicylamide] in a ratio of 85:15. The residue was dissolved in 300 ml of  $\text{Et}_2\text{O}$  and extracted with 50 ml of 1M NaOH twice, which removed the minor compound isomer (S) - 2, 5 - dimethoxy - N - [(1 - ethyl - 2 - pyrrolidinylmethyl) - 3 - propylsalicylamide from the ethereal layer. Drying and evaporation of the solvent gave 6.0 g (63%) of (S) - 5, 6 - dimethoxy - N - [(1 - ethyl - 2 - pyrrolidinylmethyl) - 3 - propylsalicylamide which was converted to 4.5 g (32%) of the L-tartarate: mp  $84-85^\circ\text{C}$  (acetone/water 98:2);  $^{13}\text{C}$  NMR (base,  $\text{CDCl}_3$ )  $\delta$  170.2, 154.9, 146.3, 143.6, 126.7, 119.9, 107.5.

The combined aqueous layer was washed with 50 ml of  $\text{Et}_2\text{O}$  twice. The pH was adjusted to 8.5 and extraction with  $\text{Et}_2\text{O}$  gave 1.3 g (14%) of pure isomer (S) - 2, 5 - dimethoxy - N - [(1 - ethyl - 2 - pyrrolidinylmethyl) - 3 - propylsalicylamide as an oil:  $^{13}\text{C}$  NMR (base,  $\text{CDCl}_3$ )  $\delta$  170.1, 151.8, 149.9, 145.8, 123.9, 115.8, 107.9.

In above,  $\beta$ -asarone isolated from *Acorus calamus* plant is found to be a starting material for salicylamide based antipsychotic drug. The use of the oil for the synthesis of drug has been reported in the art. 4-allyl-1,2,6-trimethoxybenzene (elemicin) isolated from *Cymbopogon pendulus* plant, is used as a starting material for an antibacterial drug trimethoxyprim (Shahi, A. K; Sharma, S. N. and Tava, A., J. of Essential Oil Research

9(5):561-563 (1997)). However, for the first time a plant based toxic compound  $\beta$ -asarone is found to be a starting material for the synthesis of salicylamide based antipsychotic drug.

In the development of the invention,  $\beta$ -asarone was first isolated from *Acorus calamus* and then subjected to catalytic reduction. It was then realised that isolation of  $\beta$ -asarone from *Acorus calamus* was not necessary since it was observed that direct reduction of calamus oil could be performed with the dual benefit of not requiring isolation of  $\beta$ -asarone as well as resulting in the desired product 1-Propyl-2,4,5-trimethoxybenzene with a good yield. In addition, it was found that all three asarones give the same reduced product as the chemical structures of all three asarones ( $\alpha$ ,  $\beta$  and  $\gamma$ -asarone) found in calamus oil have the same molecular formula ( $C_{12}H_{16}O_3$ ), the only difference being in the position of the double bond. The literature survey also supported the formation of same reduced dihydro products such as dihydrosafrole, dihydroeugenol, dihydroanethole and dihydrostilbene derivatives after reduction of corresponding either of the  $\alpha$ ,  $\beta$  and/or  $\gamma$ - isomers (Steffen, A., In: Perfume and Flavor Chemicals, Allured Publishing Corporation, 362 South Schmale Road, Carol Stream, IL, U.S.A. (1994) and Cushman, M.; Nagarathnam, D.; Gopal, D.; Hu-ming, H.; Lin, C. M.; and Hamel, E., J. Med. Chem. 35:2293-2306 (1992)).

It was observed during the course of development of the invention, that in fact, catalytic hydrogenation of whole calamus oil, which contains upto 90 % of asarones including  $\alpha$ ,  $\beta$  and  $\gamma$ -asarone, gave a high yield of product 1-Propyl-2,4,5-trimethoxybenzene as all three asarones produce the same reduced dihydro product. Column purification of reduced calamus oil gave 1-Propyl- 2,4,5-trimethoxybenzene with sweet and pleasant aroma. In addition, reduced calamus oil itself was found to possess a honey and rosy aroma, which is totally different from the distinctive smell of 1-Propyl-2,4,5-trimethoxybenzene. Therefore, both 1-Propyl-2,4,5-trimethoxybenzene or reduced calamus oil are capable of utilisation in flavour, perfumery and pharmaceutical industries.

There has been a lot of research on the effect of the substituents and functional groups which make a substance toxic or eliminate the toxicity. Any chemical substance that is electrophilic or metabolized to electrophilic species are often quite toxic, because electrophilic substances can react covalently with nucleophilic substituents of cellular macromolecules such as DNA, RNA, enzymes and proteins. These irreversible covalent interactions with important cellular macromolecules interfere with the macromolecule's function and can lead to a variety of toxic effects including cancer, hepatotoxicity, reproductive toxicity and developmental toxicity. It has been realised that the side chain of  $\beta$ -asarone contains carbon-carbon double

bond, which can be metabolized to epoxide. The epoxide so formed is highly electrophilic and is capable of interacting with biological tissues, and could therefore, be the reason for the toxicity of  $\beta$ -asarone. In view of the above fact, it was possible to reduce the toxicity of  $\beta$ -asarone by hydrogenating the side olefinic bond into 1-propyl-2,4,5-trimethoxybenzene having a single bond as a side chain. The toxicity of the reduced calamus oil as well as of 1-Propyl-2,4,5-trimethoxybenzene was tested. Toxicity test was performed on albino mice (body weight  $25 \pm 2$  g). 1-Propyl-2,4,5-trimethoxybenzene was administered intraperitoneally (I.P.) and the animals were observed for 24 hr. Where the initial pilot dose was lethal, the sample was diluted. This was the acute toxicity test for maximum tolerance dose (MTD) as a single dose. It was noted that 1-Propyl-2,4,5-trimethoxybenzene was nearly five times (maximum tolerant doses; 0.56 ml/kg b.w.) less toxic than  $\beta$ -asarone (0.12 ml/kg b.w.) while whole reduced (hydrogenated) calamus oil (0.20 ml/kg b.w.) had half toxicity than the calamus oil (0.10 ml/kg b.w.). It must be noted that further reduction in toxicity is possible by further dilution as the odor intensity of 1-Propyl-2,4,5-trimethoxybenzene and reduced calamus oil is substantially stronger than both  $\beta$ -asarone and calamus oil.

The above process is also applicable for not only calamus oil but also to reduce the toxicity of several other plants that are rich in  $\alpha$ ,  $\beta$  and/or  $\gamma$ -asarone, such as *Heterotropa yakusimensis* for  $\alpha$ -asarone (Saiki, Y.; Fukuyama, E. and Tsuneya, T., Yakugaku Zasshi 107(3): 219-226 (1987)) in 77%, *Asarum europaeum* for  $\beta$ -asarone (Rams, B., Herba Hungarica 22(1): 13-19 (1983)) in 70%, and *Crowea angustifolia* for  $\gamma$ -asarone (Garg, S. N., Agarwal, S. K. and Duhan, S. P. S., J. Essential Oil Research 5(2): 139-142 (1993) and Brophy J. J.; Goldsack, R. J.; Punruekpong, A.; Forster, P. I.; and Fookes, C. J. R., J. Essential Oil research 9(4):401-409 (1997)) in 68%, while obtaining a new kind of aroma.

The detailed toxicity test on animals, odour evaluation of product 1-Propyl-2,4,5-trimethoxybenzene and use of 1-Propyl-2,4,5-trimethoxybenzene as an intermediate for the synthesis of various other drugs are in progress which will further enhance the applications of the present invention as well as of *Acorus calamus* plant of tetraploid and hexaploid origin.

The following examples are given by way of illustration of the present invention and should not be construed to limit the scope of the present invention.

#### EXAMPLE 1:

Plant Material and Chemicals: The plant material was collected in March-April 1999 from Palampur (H.P.) and was confirmed as '*Acorus calamus* Linn' by comparison with the specimen (IHBT no. 1066) kept in the herbarium of our Institute. The hydrodistillation of

rhizomes of *Acorus calamus* gave pungent smelling oil in 1.7 % yield (w/w) with a presence of 81-85 %  $\beta$ -asarone (by GC).  $\alpha$ -asarone is procured from Sigma chemicals (U.S.A) and is used as an authentic sample.

**Isolation of  $\beta$ -asarone from *Acorus calamus*:** The pale yellow calamus oil (17.00 g) was chromatographed over silica gel using hexane as eluent to remove unwanted non-polar compounds. Subsequent elution with hexane-benzene mixture with increasing proportion of benzene gave a pure liquid 13.94 g in 82 % yield (w/w) with  $R_f$  0.63 on silica gel TLC plate (hexane: benzene/toluene: ethylacetate:: 1:1:0.1) whose electrospray (ES)-mass spectrum gave a molecular ion at  $m/e$  208 ( $M^+$ , 100), 193 ( $M^+ - Me$ , 46), 165 ( $M^+ - C_3H_7$ , 24), suggesting the molecular formula  $C_{12}H_{16}O_3$  in good agreement with the observation of 12 signals with peak at  $\delta$  125.5 (C-1'), 124.7 (C-2') and 14.5 (C-3') for side propenyl group and rest carbons at 151.4 (C-2), 148.5 (C-4), 142.3 (C-5), 118.0 (C-1), 114.1 (C-6), 97.6 (C-3) and 56.5, 56.2 & 55.9 (3-OCH<sub>3</sub>) on the  $^{13}C$  NMR (CDCl<sub>3</sub>, 75.4 MHz). The IR spectrum showed strong absorption at 1608  $cm^{-1}$ , indicating the presence of an olefinic group and rest are at 2937, 2835, 1583, 1512, 1465, 1321, 1213, 1119, 1037, 965 and 859  $cm^{-1}$ . The  $^1H$  NMR (CDCl<sub>3</sub>, 300 MHz) signals showed a dd at  $\delta$  6.50 (1H,  $J=15.8$  Hz and 1.5 Hz, H-1'), dq at 5.78 (1H,  $J=6.5$  Hz and 15.8 Hz, H-2') and 1.85 (3H, dd,  $J=6.5$  Hz and 1.5 Hz, H-3') due to proton of propenyl side chain and rest protons at 6.84 (1H, s, H-6), 6.53 (1H, s, H-3), and 3.88, 3.83 and 3.79 (s, 3H, each, 3-OCH<sub>3</sub>). UV  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 269 (2.36), 301 (4.01). On the basis of above spectral data and comparing with reported literature (Gonzalez, M. C., Sentandreu, M. A.; Rao, K. S.; Zafra, M. C. and Cortes, D., *Phytochemistry* 43:1361-1364 (1996)), the liquid was identified as  $\beta$ -asarone in 94% purity (by GC) (Fig. 2)

**Synthesis of 1-Propyl-2,4,5-trimethoxybenzene from  $\beta$ -asarone:** The  $\beta$ -asarone (6.00 g, 0.029 mol) in 160 ml of ethanol is stirred with 10% palladium on activated charcoal (0.80 g) and ammonium formate (17.00 g, 0.27 mol) at room temperature under nitrogen atmosphere till the disappearance of starting material. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water and the ethyl acetate layer washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. Evaporation of filtrate left a liquid, which was chromatographed, on silica gel using hexane-benzene mixture with increasing proportion of benzene as the eluent. The eluate was evaporated to give 5.87 g (97%) of a clear sweet and pleasant liquid with  $R_f$  0.69 (hexane: benzene/toluene: ethylacetate:: 1:1:0.1) which solidified below 0° C. The  $^1H$  NMR (DMSO-d<sub>6</sub>) of liquid showed an expected shift of proton of propyl side chain which appeared at  $\delta$  d



2.5 (2H, t, C-1'), 1.6 (2H, m, C-2') and 0.9 (3H, t, C-3') and rest protons at 6.72 (1H, s, H-6), 6.62 (1H, s, H-3) and 3.76 to 3.68 (9H, s, 3-OCH<sub>3</sub>). The mass spectrum of liquid showed a molecular ion at m/e 210 (M<sup>+</sup>, 39), 181 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>, 100), 167 (M<sup>+</sup> - C<sub>3</sub>H<sub>7</sub>, 5), 151 (M<sup>+</sup> - OCH<sub>3</sub> + CO, 29), 136 (M<sup>+</sup> - C<sub>3</sub>H<sub>7</sub> + OCH<sub>3</sub>, 10) which IR spectrum showed strong absorption at 2958, 2870, 1512, 1464, 1398, 1205, 1124, 1040, 978 and 843 cm<sup>-1</sup> with disappearance of olefinic absorption (1608 cm<sup>-1</sup>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) of liquid also showed expected shift of propyl side signals of C-1', C-2' and C-3' which appeared at δ 31.6 (C-1'), 23.3 (C-2') and 13.79 (C-3') and rest at δ 151.4 (C-2), 147.4 (C-4), 142.7 (C-5), 122.7 (C-1), 114.3 (C-6), 98.0 (C-3) and 56.5, 56.2 & 56.0 (3-OCH<sub>3</sub>). UV λ<sub>max</sub> MeOH nm (log ε): 288 (4.28). A shift by 13 nm in UV-vis spectra of product was observed from 301 nm to 288 nm (as conjugation of double bond of starting material asarone was reduced to single bond) with complete disappearance of peak 269 nm (Fig 1). On the basis of <sup>1</sup>H NMR (Fig. 4), <sup>13</sup>C NMR (Fig. 5) and Mass (Fig. 6) spectral data, the above liquid was identified as 1-Propyl-2,4,5-trimethoxybenzene in 99 % purity (by GC) (Fig. 3).

#### Synthesis of 1-Propyl-2,4,5-trimethoxybenzene from crude oil of *Acorus calamus*:

In this method 42.00 g of crude calamus oil in 300 ml methanol was hydrogenated with 10 % Pd/C (4.80 g) at 10-40 psi at room temperature till the disappearance of starting material. The catalyst was filtered and the solvent was removed under reduced pressure, which afforded 39.9 g (95 w/v) of reduced oil. Column purification of reduced oil on silica gel column using above eluent system (hexane-benzene mixture) gave a liquid 35.76 g in 85 % yield (w/v). The <sup>1</sup>H NMR (CDCl<sub>3</sub>) of liquid appeared at δ d 2.4 (2H, t, C-1'), 1.6 (2H, m, C-2'), 0.9 (3H, t, C-3'), 6.81 (1H, s, H-6), 6.32 (1H, s, H-3) and 3.84 to 3.78 (9H, s, 3-OCH<sub>3</sub>). The GC, Mass spectra and UV-vis spectra of liquid confirmed the formation of 1-Propyl-2,4,5-trimethoxybenzene of formula I.

#### The main advantages of the present invention are

1. A simple and economical process to convert an internationally banned toxic compound β-asarone or calamus oil into useful and less toxic products.
2. Introduction of a new kind of sweet, fruity, rosy and spicy aroma molecule better than the original pungent smell of calamus oil for application in flavour, perfumery and pharmaceutical industries.
3. Discovery of a product 1-Propyl-2,4,5-trimethoxybenzene as an inexpensive and simple starting material for salicylamide based antipsychotic drug.

4. The present chemical process can increase the price of calamus oil as demand of new products go up as presently, calamus oil of tetraploid or hexaploid varieties distributed extensively in Asian origin) has very low price in comparison to the oil of diploid and triploid (distributed in American or European origin) varieties.
5. A process of converting asarones rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis* into useful and non-toxic products.
6. A simple process by which a toxic compound  $\beta$ -asarone present upto 70 to 90 % in tetraploid or hexaploid varieties (distributed extensively in Asian countries) of *Acorus calamus* is converted into useful product 1-Propyl-2, 4,5-trimethoxybenzene.
7. A simple process for isolation of  $\beta$ -asarone in high purity from *Acorus calamus* oil by column chromatography affording above 90% purity, more than the purity (70%) claimed by Aldrich and Fluka catalog chemicals.
8. A simple process for the preparation of 1-Propyl-2, 4, 5-trimethoxybenzene by catalytic reduction of above isolated  $\beta$ -asarone.
9. An inexpensive process for the preparation of 1-Propyl-2, 4,5-trimethoxybenzene by direct reduction of calamus oil in which percentage of asarones (including  $\alpha$ ,  $\beta$  and  $\gamma$ -asarone) go up to 90 percentage in tetraploid or hexaploid varieties of *Acorus calamus* oil.
10. Scope for commercialisation of a product 1-Propyl-2, 4,5-trimethoxybenzene and reduced calamus oil in flavour, perfumery and pharmaceutical industries, since both products have a new kind of sweet, fruity, spicy and honey and rosy aroma respectively.
11. A process for minimizing the toxicity of an internationally banned calamus oil of tetraploid or hexaploid varieties for re-utilisation as toxicity of the reduced calamus oil and 1-Propyl-2, 4,5-trimethoxybenzene is found to be two to five times less than calamus oil and  $\beta$ -asarone respectively.
12. A single step process to obtain two fold benefits by reduction in toxicity and improvement in aroma better than the original pungent aroma of calamus oil.
13. 1-Propyl-2, 4,5- trimethoxybenzene is an inexpensive, high yielding and simple starting material for important 3-propyl-5, 6-dimethoxysalicylamide based antipsychotic drug. The reported prior art synthesis of salicylamide derivative requires several steps in which intermediate 1-Propyl-2, 4,5-trimethoxybenzene itself is

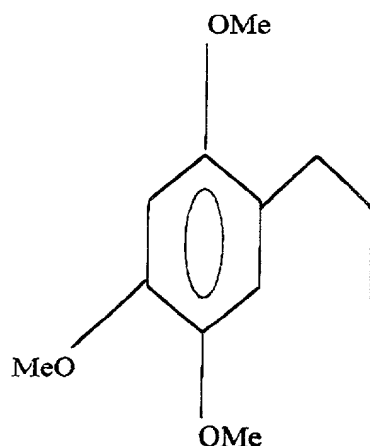
synthesised in two steps by using Friedel-Craft acylation of an expensive material 1,2,4-trimethoxybenzene with propylchloride followed by reduction.

14. Provide above simple process of reduction to convert other asarone rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis* into useful products such as 1-Propyl-2, 4,5-trimethoxybenzene.

U 012930-9

**We claim:**

1. A process for the preparation of 1-Propyl-2, 4, 5-trimethoxybenzene of the formula I useful as a aroma molecule and as a starting material and intermediate for preparation of various drugs,



the said process comprising the steps of

- (a) providing crude calamus oil or  $\beta$ -asarone in a solvent selected from the group consisting of ethanol, methanol, THF, DCM, toluene, and chloroform;
  - (b) hydrogenation of the solution in the presence of a catalyst selected from the group consisting of Pd/C, Pt, Pd(OH)<sub>2</sub>, Raney nickel and ammonium formate at a pressure in the range of 10 – 40 psi hydrogen gas and at a temperature in the range of 15 - 40°C;
  - (c) filtering the catalyst and removing the solvent under reduced pressure in the range of 10 – 100 mm Hg;
  - (d) subjecting the reduced calamus oil to column of silica gel chromatography using an eluent to obtain the desired product in liquid form with 85 – 97 % purity.
2. A process as claimed in claim 1 wherein the catalyst comprises 5 - 10 % Pd/C.
  3. A process as claimed in claim 1 wherein the calamus oil used is of tetraploid or hexaploid origin.
  4. A process as claimed in claim 1 wherein the toxicity of the hydrogenated calamus oil is two times less than that of the starting calamus oil.
  5. A process as claimed in claim 1 wherein the reduced calamus oil has a novel honey and roses aroma.
  6. A process as claimed in claim 1 wherein the 1-Propyl-2,4,5-trimethoxybenzene obtained has a novel sweet, ylang, slightly spicy and fruity aroma.

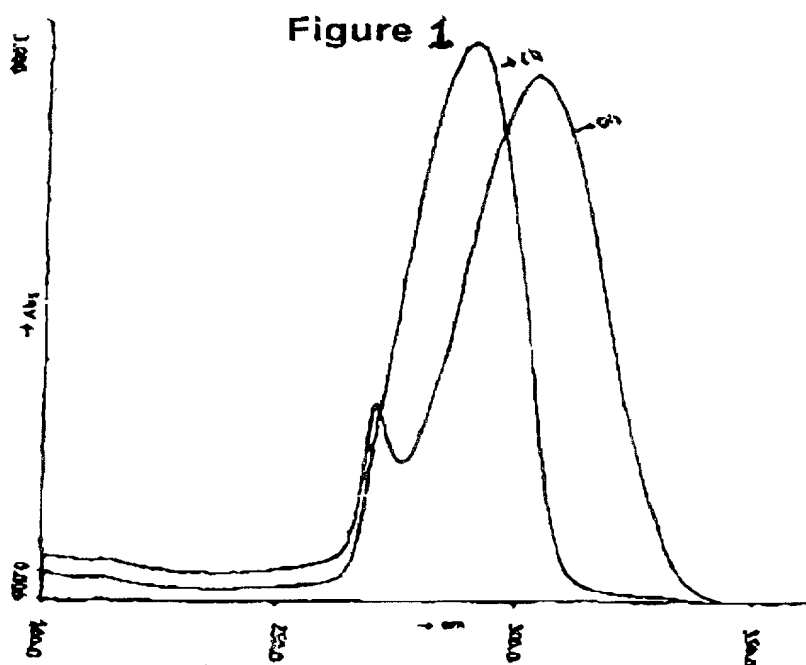
7. A process as claimed in claim 1 wherein the calamus oil is extracted from asarone rich plants such as *Asarum europaeum*, *Crowea angustifolia* and *Heterotropa yakusimensis*.
8. Use of reduced calamus oil in toiletry soap, shaving cream and tobacco products.
9. Use of 1-Propyl-2,4,5-trimethoxybenzene as a multipurpose additive in mouthwash, tooth paste, antiseptic soap products, chewing gum flavour and in spicy products.
10. Use of 1-Propyl-2,4,5-trimethoxybenzene as an inexpensive and simple starting material for the preparation of 3-propyl -5,6-dimethoxysalicylamide based antipsychotic drug 5, 6 - dimethoxy - N [(1 - ethyl - 2 - pyrrolidinyl) methyl] - 3 - propylsalicylamide
11. Use of 1-Propyl-2,4,5-trimethoxybenzene to obtain products for use as flavour, in perfumery industries and as starting material for various important drugs and for new organic compounds by bromination, oxidation, reduction, coupling reaction, allylic hydroxylation, dimerisation, formylation, Grignard reaction, oxymercuration-demercuration, demethylation, alkylation and epoxidation.
12. A process for the preparation of 5, 6 - dimethoxy - N [(1 - ethyl - 2 - pyrrolidinyl) methyl] - 3 - propylsalicylamide from 1-Propyl-2, 4, 5-trimethoxybenzene of the formula I.

**U 012930-9**

## ABSTRACT

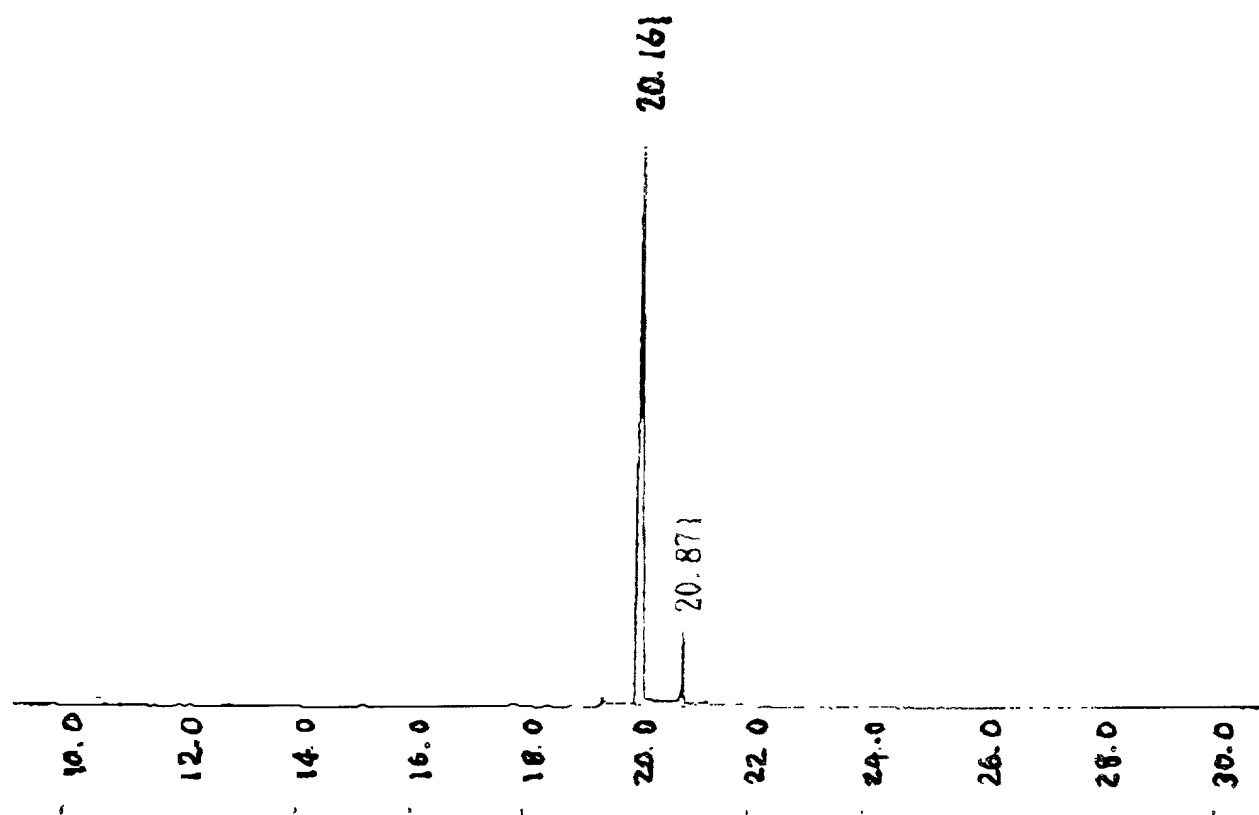
The invention relates to a process for the preparation of 1-Propyl-2, 4, 5-trimethoxybenzene useful as a aroma molecule and as a starting material and intermediate for preparation of various drugs. The process comprises providing crude calamus oil or  $\beta$ -asarone in a solvent; hydrogenating the solution in the presence of a catalyst; filtering the catalyst and removing the solvent under reduced pressure; subjecting the reduced calamus oil to column of silica gel chromatography using an eluent to obtain the desired product in liquid form with 85 – 97 % purity.

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2
--	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	---



UV-vis spectra of (i) 1-Propyl-2,4,5-trimethoxybenzene and its comparison with (ii)  $\beta$ -asarone (2,4,5-trimethoxy-1-propenylbenzene).

Figure 2



Gas Chromatogram of  $\beta$ -asarone with minor presence of  $\alpha$ -asarone



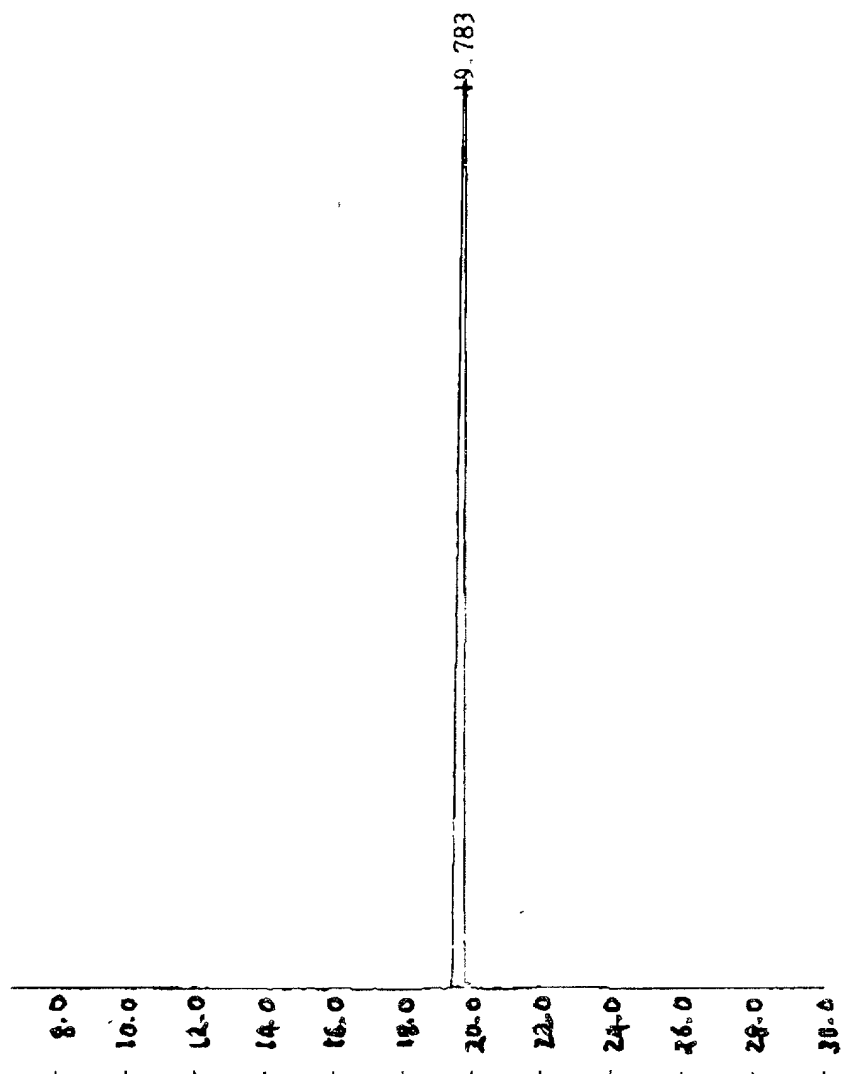
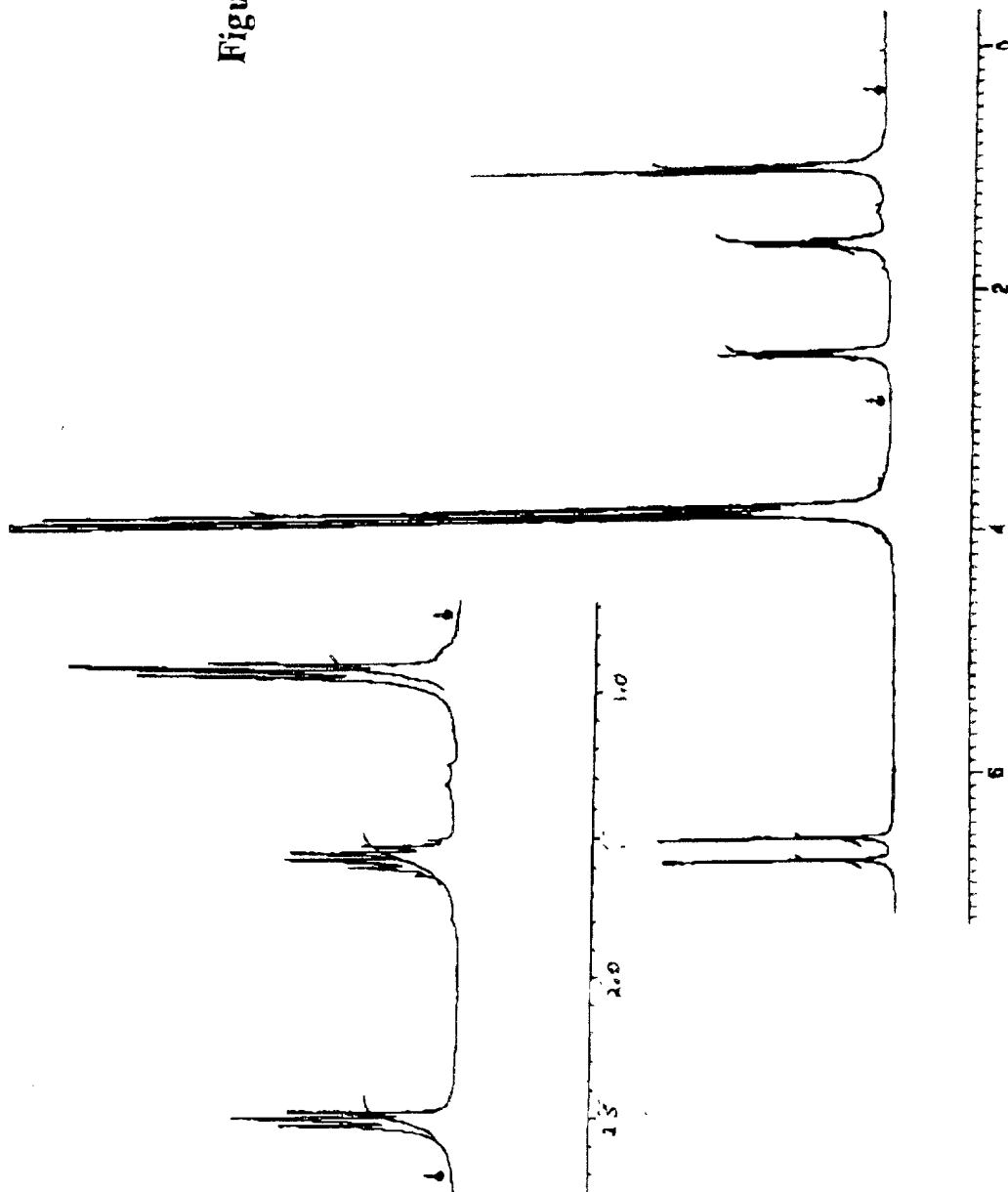
**Figure 3****Gas Chromatogram of 1-Propyl-2,4,5-trimethoxybenzene**

Figure 4



$^1\text{H-NMR}$  (300 MHz) spectra of 1-Propyl-2,4,5-trimethoxybenzene in  $\text{CDCl}_3$

Figure 5

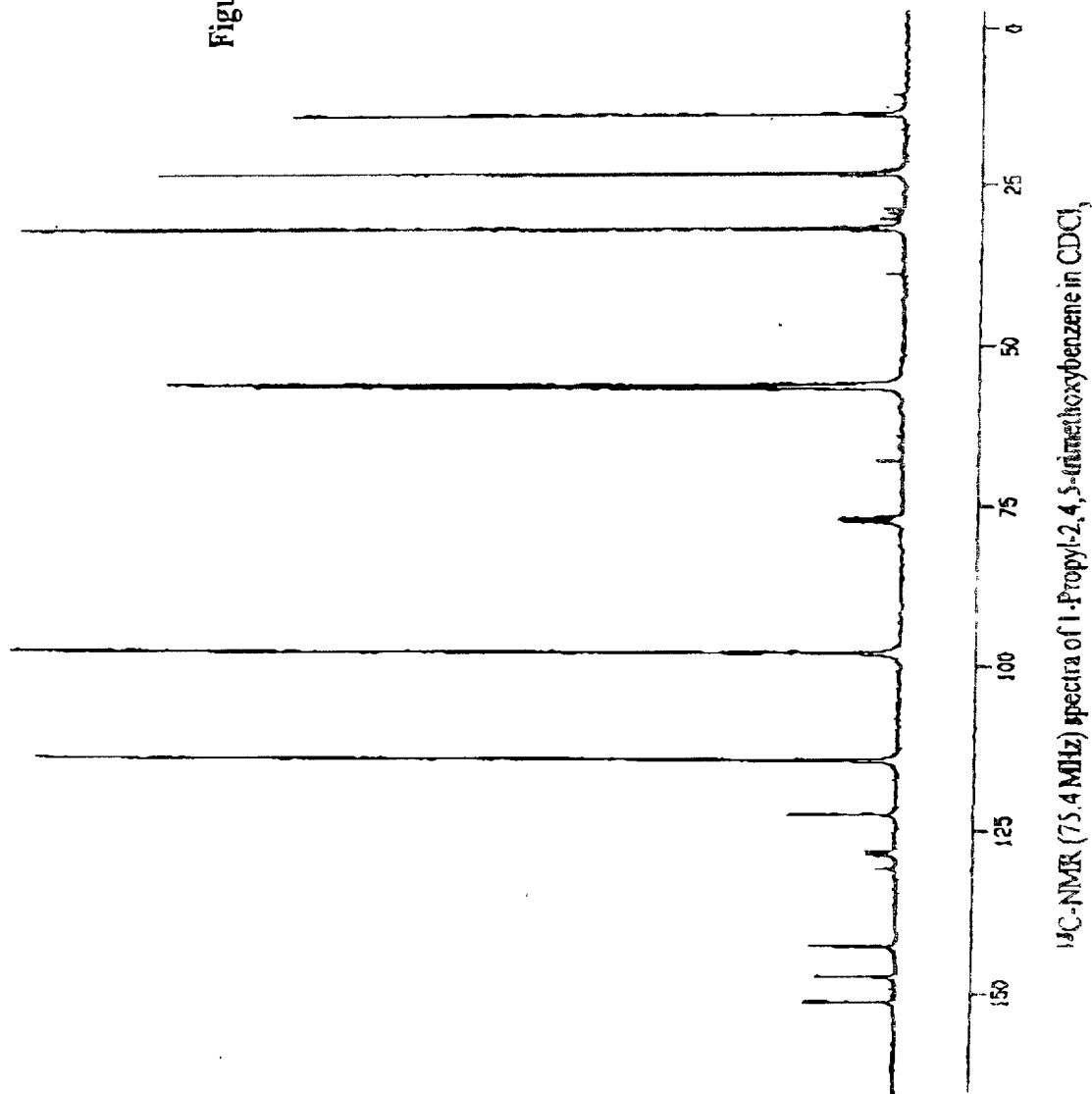


Figure 6

